

## WHAT IS CLAIMED IS:

1. An acid resistant oligonucleotide targeted to an RNA encoding a phosphodiesterase 4 (PDE4) protein selected from the group consisting of SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50 and SEQ ID NO:51, said oligonucleotide comprising:

a polymer of nucleotides, said polymer having a nucleic acid backbone structure modified from that of a naturally occurring nucleotide polymer; and

a blocking chemical modification at or near at least the 3' end of the polymer;

wherein the oligonucleotide is characterized by a pH stability of at least one hour at a pH of about 0.01 to about 10 and a nuclease resistance of at least twice that of a naturally occurring polymer having the same number of nucleotides.

2. The oligonucleotide of claim 1, wherein the oligonucleotide has from about one to about 100 nucleotides.

3. The oligonucleotide of claim 1, wherein the oligonucleotide is completely or partially derivatized by a chemical moiety selected from the group consisting of: phosphodiester linkages, phosphotriester linkages, phosphoramidate linkages, siloxane linkages, carbonate linkages, carboxymethylester linkages, acetamidate linkages, carbamate linkages, thioether linkages, bridged phosphoramidate linkages, bridged methylene phosphonate linkages, phosphorothioate linkages, methylphosphonate linkages, phosphorodithioate linkages, morpholino, bridged phosphorothioate linkages, sulfone internucleotide linkages, 3'-3' linkages, 5'-2' linkages, 5'-5' linkages, 2'-deoxy-erythropentofuranosyl, 2'-fluoro, 2'-O-alkyl nucleotides, 2'-O-alkyl-n(O-alkyl) phosphodiester, 2'-O-methyl nucleotides, morpholino linkages, p-ethoxy oligonucleotides, PNA linkages, p-isopropyl oligonucleotides, butanol, butyl, and phosphoramidates

5           4. The oligonucleotide of claim 1, wherein the oligonucleotide has a sequence selected from the group consisting of: SEQ ID NO: 1; SEQ ID NO: 2; SEQ ID NO: 3; SEQ ID NO: 4; SEQ ID NO: 5; SEQ ID NO: 6; SEQ ID NO: 7; SEQ ID NO: 8; SEQ ID NO: 9; SEQ ID NO: 10; SEQ ID NO: 11; SEQ ID NO: 12; SEQ ID NO: 13; SEQ ID NO: 14; SEQ ID NO: 15; SEQ ID NO: 16; SEQ ID NO: 17; SEQ ID NO: 18; SEQ ID NO: 19; SEQ ID NO: 20; SEQ ID NO: 21; SEQ ID NO: 22; SEQ ID NO: 23; SEQ ID NO: 24; SEQ ID NO: 25; SEQ ID NO: 26; SEQ ID NO: 27; SEQ ID NO: 28; SEQ ID NO: 29; SEQ ID NO: 30; SEQ ID NO: 31; SEQ ID NO: 32; SEQ ID NO: 33; SEQ ID NO: 34; SEQ ID NO: 35; SEQ ID NO: 36; SEQ ID NO: 37; SEQ ID NO: 38; SEQ ID NO: 39; SEQ ID NO: 40; SEQ ID NO: 41; SEQ ID NO: 42; SEQ ID NO: 43; SEQ ID NO: 44; and SEQ ID NO: 45.

10           5. The oligonucleotide of claim 1, wherein the oligonucleotide binds selectively to exon/intron boundaries and splice sites of RNA.

15           6. The oligonucleotide of claim 1, wherein the oligonucleotide binds selectively to an mRNA encoding a phosphodiesterase E4 protein.

20           7. An acid resistant oligonucleotide that binds selectively to DNA involved in phosphodiesterase 4 (PDE4) expression, said oligonucleotide comprising:

25           a polymer of nucleotides, said polymer having a nucleic acid backbone structure modified from that of a naturally occurring nucleotide polymer; and

            a blocking chemical modification at or near at least the 3' end of the polymer;

            wherein the oligonucleotide is characterized by a pH stability of at least one hour at a pH of about 0.1 to about 10 and a nuclease resistance of at least twice that of a naturally occurring polymer having the same number of nucleotides.

5           8. The oligonucleotide of claim 7, wherein the DNA is selected from the group consisting of : PDE4 coding sequences, PDE4 promoter sequences, and PDE4 enhancer sequences.

10           9. The oligonucleotide of claim 7, wherein the oligonucleotide has from about one to about 100 nucleotides.

15           10. The oligonucleotide of claim 7, wherein the oligonucleotide is completely or partially derivatized by a chemical moiety selected from the group consisting of: phosphodiester linkages, phosphotriester linkages, phosphoramidate linkages, siloxane linkages, carbonate linkages, carboxymethylester linkages, acetamidate linkages, carbamate linkages, thioether linkages, bridged phosphoramidate linkages, bridged methylene phosphonate linkages, phosphorothioate linkages, methylphosphonate linkages, phosphorodithioate linkages, morpholino, bridged phosphorothioate linkages, sulfone internucleotide linkages, 3'-3' linkages, 5'-2' linkages, 5'-5' linkages, 2'-deoxy-erythropentofuranosyl, 2'-fluoro, 2'-O-alkyl nucleotides, 2'-O-alkyl-n(O-alkyl) phosphodiester, 2'-O-methyl nucleotides, morpholino linkages, p-ethoxy oligonucleotides, PNA linkages, p-isopropyl oligonucleotides, butanol, butyl, and phosphoramidates.

20           11. A pharmaceutical composition comprised of an acid resistant oligonucleotide that binds selectively to an mRNA encoding a phosphodiesterase 4 protein, said oligonucleotide comprising a polymer having a nucleic acid backbone structure modified from that of a naturally occurring nucleotide polymer and a blocking chemical modification at or near at least one end of the polymer; and

25           a pharmaceutically acceptable carrier;

30           wherein the oligonucleotide is characterized by a pH stability of at least one hour at a pH of about 0.01 to about 10 and a nuclease resistance of at least twice that of a naturally occurring polymer having the same number of nucleotides.

5           12. The pharmaceutical composition of claim 11, wherein the nucleic acid is an  
oligonucleotide having from about one to about 100 nucleotides.

10           13. The pharmaceutical composition of claim 12, wherein said nucleic acid is linked to a  
compound selected from the group consisting of protein, amino acid, lipid, sugar, glycoprotein,  
antibiotic, organic compound, organometallic compound, steroid, and metal.

14. The pharmaceutical composition of claim 11, wherein said nucleic acid is protonated.

15           15. The pharmaceutical composition of claim 11, wherein the oligonucleotide has been  
protonated/acidified to have a pH at or below 7.

16. The pharmaceutical composition of claim 11, wherein the nucleic acid is  
encapsulated in a liposome.

20           17. A pharmaceutical composition comprised of an acid resistant oligonucleotide that  
binds selectively to DNA involved in phosphodiesterase 4 expression, said oligonucleotide  
comprising a polymer having a nucleic acid backbone structure modified from that of a naturally  
occurring nucleotide polymer and a blocking chemical modification at or near at least one end of  
the polymer; and

25           a pharmaceutically acceptable carrier;

wherein the oligonucleotide is characterized by a pH stability of at least one hour at a pH  
of about 0.1 to about 10 and a nuclease resistance of at least twice that of a naturally occurring  
polymer having the same number of nucleotides.

30           18. The pharmaceutical composition of claim 17, wherein the nucleic acid is an  
oligonucleotide having from about one to about 100 nucleotides.

5 19. The pharmaceutical composition of claim 17, wherein said nucleic acid is linked to a compound selected from the group consisting of protein, amino acid, lipid, sugar, glycoprotein, antibiotic, organic compound, organometallic compound, steroid, and metal.

10 20. The pharmaceutical composition of claim 17, wherein said nucleic acid is protonated.

21. The pharmaceutical composition of claim 20, wherein the oligonucleotide has been protonated/acidified to have a pH at or below 7.

15 22. The pharmaceutical composition of claim 17, wherein the nucleic acid is encapsulated in a liposome.

20 23. A method of treating a mammal comprising topically administering to a site of need a therapeutically effective amount of an acid resistant oligonucleotide that binds selectively to an mRNA encoding a phosphodiesterase 4 protein, said oligonucleotide comprising a polymer having a nucleic acid backbone structure modified from that of a naturally occurring nucleotide polymer and a blocking chemical modification at or near at least the 3' end of the polymer;

25 wherein the oligonucleotide is characterized by a pH stability of at least one hour at a pH of about 0.01 to about 10 and a nuclease resistance of at least twice that of a naturally occurring polymer having the same number of nucleotides.

30 24. The method of claim 11, wherein the polymer is completely or partially derivatized by a chemical moiety selected from the group consisting of: phosphodiester linkages, phosphotriester linkages, phosphoramidate linkages, siloxane linkages, carbonate linkages, carboxymethylester linkages, acetamidate linkages, carbamate linkages, thioether linkages, bridged phosphoramidate linkages, bridged methylene phosphonate linkages, phosphorothioate

5 linkages, methylphosphonate linkages, phosphorodithioate linkages, morpholino, bridged  
phosphorothioate and/or sulfone internucleotide linkages, 3'-3' linkages, 2'-5' linkages, 5'-5'  
linkages, 2'-deoxy-erythropentofuranosyl, 2'-fluoro, 2'-O-alkyl nucleotides, 2'-O-alkyl-n(O-alkyl)  
phosphodiester, 2'-O-methyl nucleotides, morpholino linkages, p-ethoxy oligonucleotides, PNA  
linkages, p-isopropyl oligonucleotides, butanol, butyl, and phosphoramidates.

10 25. The method of claim 23, wherein the oligonucleotide is protonated.

15 26. The method of claim 23, wherein the PDE4 is selected from the group consisting of  
SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50 and SEQ ID  
NO:51.

20 27. The method of claim 23 wherein the oligonucleotide is administered to a mammal  
suffering from a disease or disorder selected from the group consisting of: atopic dermatitis,  
allergic rhino-conjunctivitis, T cell mediated dermatitis, B-cell mediated dermatitis, and acute  
wheal and flare reaction.

25 28. A method of treating a mammal comprising topically administering to a site of need  
a therapeutically effective amount of an acid resistant oligonucleotide that binds selectively to  
DNA involved in phosphodiesterase 4 expression, said oligonucleotide comprising a polymer  
having a nucleic acid backbone structure modified from that of a naturally occurring nucleotide  
polymer and a blocking chemical modification at or near at least the 3' end of the polymer;

30 wherein the oligonucleotide is characterized by a pH stability of at least one hour at a pH  
of about 0.1 to about 10 and a nuclease resistance of at least twice that of a naturally occurring  
polymer having the same number of nucleotides.

5           29. The method of claim 28, wherein the DNA involved in phosphodiesterase 4  
expression is selected from the group consisting of: PDE4 coding sequences, PDE4 promoter  
sequences, and PDE4 enhancer sequences.

10           30. The method of claim 28, wherein the polymer is completely or partially derivatized  
by a chemical moiety selected from the group consisting of: phosphodiester linkages,  
phosphotriester linkages, phosphoramidate linkages, siloxane linkages, carbonate linkages,  
carboxymethylester linkages, acetamidate linkages, carbamate linkages, thioether linkages,  
bridged phosphoramidate linkages, bridged methylene phosphonate linkages, phosphorothioate  
15 linkages, methylphosphonate linkages, phosphorodithioate linkages, morpholino, bridged  
phosphorothioate and/or sulfone internucleotide linkages, 3'-3' linkages, 2'-5' linkages, 5'-5'  
linkages, 2'-deoxy-erythropentofuranosyl, 2'-fluoro, 2'-O-alkyl nucleotides, 2'-O-methyl  
nucleotides, 2'-O-alkyl-n(O-alkyl) phosphodiesters, morpholino linkages, p-ethoxy  
oligonucleotides, PNA linkages, p-isopropyl oligonucleotides, butanol, butyl, and  
phosphoramidates and phosphoramidates.

20           31. The method of claim 28, wherein the oligonucleotide is protonated.

25           32. A method of treating a mammal comprising intranasally administering a  
therapeutically effective amount of an acid resistant oligonucleotide that binds selectively to an  
mRNA encoding a phosphodiesterase 4 protein, said oligonucleotide comprising a polymer  
having a nucleic acid backbone structure modified from that of a naturally occurring nucleotide  
polymer and a blocking chemical modification at or near at least the 3' end of the polymer;  
wherein the oligonucleotide is characterized by a pH stability of at least one hour at a pH  
of about 0.01 to about 10 and a nuclease resistance of at least twice that of a naturally occurring  
30 polymer having the same number of nucleotides.

5 33. The method of claim 32, wherein the polymer is completely or partially derivatized  
by a chemical moiety selected from the group consisting of: phosphodiester linkages,  
phosphotriester linkages, phosphoramidate linkages, siloxane linkages, carbonate linkages,  
carboxymethylester linkages, acetamidate linkages, carbamate linkages, thioether linkages,  
bridged phosphoramidate linkages, bridged methylene phosphonate linkages, phosphorothioate  
10 linkages, methylphosphonate linkages, phosphorodithioate linkages, morpholino, bridged  
phosphorothioate and/or sulfone internucleotide linkages, 3'-3' linkages, 2'-5' linkages, 5'-5'  
linkages, 2'-deoxy-erythropentofuranosyl, 2'-fluoro, 2'-O-alkyl nucleotides, 2'-O-alkyl-n(O-alkyl)  
phosphodiester, 2'-O-methyl nucleotides, morpholino linkages, p-ethoxy oligonucleotides, PNA  
linkages, p-isopropyl oligonucleotides, butanol, butyl, and phosphoramidates.

15 34. The method of claim 32, wherein the oligonucleotide is protonated.

20 35. The method of claim 32, wherein the PDE4 is selected from the group consisting of:  
SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50 and SEQ ID  
NO:51.

25 36. The method of claim 35, wherein the oligonucleotide has a sequence selected from  
the group consisting of: SEQ ID NO: 1; SEQ ID NO: 2; SEQ ID NO: 3; SEQ ID NO: 4; SEQ ID  
NO: 5; SEQ ID NO: 6; SEQ ID NO: 7; SEQ ID NO: 8; SEQ ID NO: 9; SEQ ID NO: 10; SEQ ID  
NO: 11; SEQ ID NO: 12; SEQ ID NO: 13; SEQ ID NO: 14; SEQ ID NO: 15; SEQ ID NO: 16;  
SEQ ID NO: 17; SEQ ID NO: 18; SEQ ID NO: 19; SEQ ID NO: 20; SEQ ID NO: 21;  
SEQ ID NO: 22; SEQ ID NO: 23; SEQ ID NO: 24; SEQ ID NO: 25; SEQ ID NO: 26; SEQ ID  
NO: 27; SEQ ID NO: 28; SEQ ID NO: 29; SEQ ID NO: 30; SEQ ID NO: 31; SEQ ID NO: 32;  
SEQ ID NO: 33; SEQ ID NO: 34; SEQ ID NO: 35; SEQ ID NO: 36; SEQ ID NO: 37; SEQ ID  
30 NO: 38; SEQ ID NO: 39; SEQ ID NO: 40; SEQ ID NO: 41; SEQ ID NO: 42; SEQ ID NO: 43;  
SEQ ID NO: 44; and SEQ ID NO: 45.

5           37. The method of claim 35, wherein the oligonucleotide is administered to a mammal suffering from a disease or disorder selected from the group consisting of: atopic dermatitis, allergic rhino-conjunctivitis, T cell mediated dermatitis, B-cell mediated dermatitis, and acute wheal and flare reaction.

10           38. A method of treating a mammal comprising intranasally administering a therapeutically effective amount of an acid resistant oligonucleotide that binds selectively to DNA involved in phosphodiesterase 4 expression, said oligonucleotide comprising a polymer having a nucleic acid backbone structure modified from that of a naturally occurring nucleotide polymer and a blocking chemical modification at or near at least the 3' end of the polymer;

15           wherein the oligonucleotide is characterized by a pH stability of at least one hour at a pH of about 0.1 to about 10 and a nuclease resistance of at least twice that of a naturally occurring polymer having the same number of nucleotides.

20           39. The method of claim 38, wherein the DNA involved in phosphodiesterase 4 expression is selected from the group consisting of: PDE4 coding sequences, PDE4 promoter sequences, and PDE4 enhancer sequences.

25           40. The method of claim 38, wherein the polymer is completely or partially derivatized by a chemical moiety selected from the group consisting of: phosphodiester linkages, phosphotriester linkages, phosphoramidate linkages, siloxane linkages, carbonate linkages, carboxymethylester linkages, acetamidate linkages, carbamate linkages, thioether linkages, bridged phosphoramidate linkages, bridged methylene phosphonate linkages, phosphorothioate linkages, methylphosphonate linkages, phosphorodithioate linkages, morpholino, bridged phosphorothioate and/or sulfone internucleotide linkages, 3'-3' linkages, 2'-5' linkages, 5'-5' linkages, 2'-deoxy-erythropentofuranosyl, 2'-fluoro, 2'-O-alkyl nucleotides, 2'-O-methyl nucleotides, 2'-O-alkyl-n(O-alkyl) phosphodiester, morpholino linkages, p-ethoxy

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5 oligonucleotides, PNA linkages, p-isopropyl oligonucleotides, butanol, butyl, and phosphoramidates and phosphoramidates.

41. The method of claim 38, wherein the oligonucleotide is protonated.

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